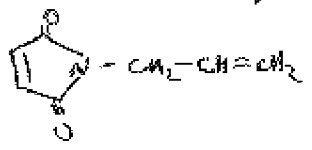
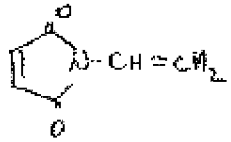
TITLE Idea Crosslinking accelerators Project No. _____ Book No. 2687 20

From Page No. ... see page 16

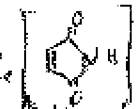
A simple N-Vinyl crosslinker, shown below may act as accelerators for matrix applications are shown below.



N-allyl maleimide



N-Vinyl maleimide

A sample of maleimide  was given to M. Buchstaber to test as an accelerator for matrix forming.

To Page No. .....

Witnessed & Understood by me,	Date	Invented by	Date
		Recorded by	

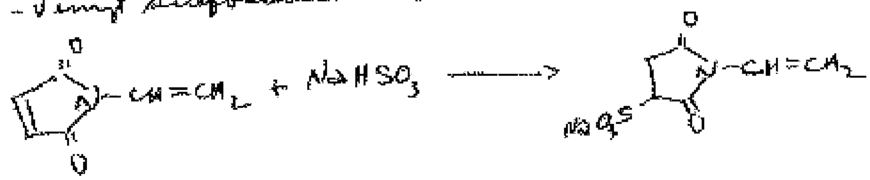
Exhibit 1

Project No. ______
Book No. ______

TITLE Idea

From Page No. ...

Ron Ofstead suggested converting N-Vinyl-maleimide to N-Vinyl sulfosuccinimide



To Page No. ......

Witnessed & Understood by me,

Date

Invented by

Date

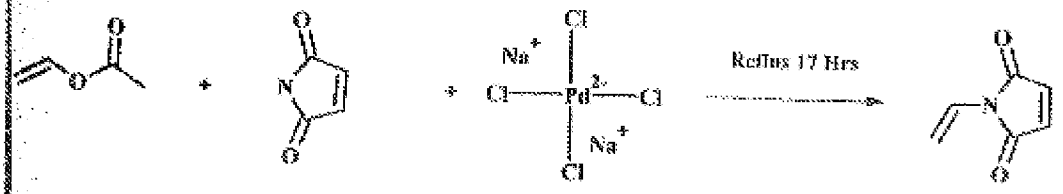
Recorded by

Exhibit 2

Title: Vinyl-Maleimide Project No. TPM 0100
Book No. 2706 21

From Page No. 586

Vinyl-Maleimide.SK2



86.089 g/mole	97.072 g/mole	294.210 g/mole	123.109 g/mole
35.5 g (~38 ml)	10 g	0.25 g	12.7 g (theory)
412.0 mmole	103.0 mmole	0.85 mmole	103.0 mmole (theory)

In a 100 ml RB flask with magnetic stir bar & reflux condenser were placed 10.0085 g maleimide (Lot # 90009887), 0.2490 g Na_2PdCl_4 & 35.5 g vinylacetate (Lot # 10221 DG). Stir & heat to refluxing. Refluxing started at 8.50 a.m. Boil. point of vinyl acetate = 72-73°C
At 1.30 p.m. – Rx turn to dark red with some solid(s) Continue refluxing to total 17 hours.

Refluxing stop at 1.50 p.m – should be short 2 hrs off
7 a.m. – Rx was still refluxing.
Remove heating & let cool. Filter off Rx remove excess of vinylacetate on a Rotovap at T = 40°C under air bleeding into the flask.
We got ~15 g residue in the flask. Add 45 ml H_2O, stir in IPA-dry ice bath at T = -20°C for 30 min. Filter off solid, dry at RT under water aspirator for to give 5.0 g yellow crystals 2706-21/22

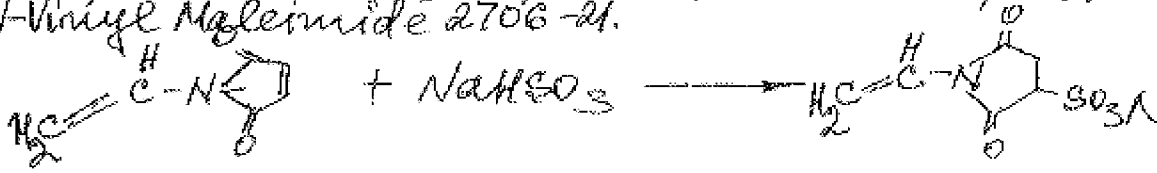
To Page No. 22

Witnessed & Understood by me,	Date	Invented by	Date
Dal Ivan		Recorded by P. Tetlenay	

Exhibit 3

From Page No. _

Rx #1 similar as Rx #3 in NMR tube, but using N-Vinyl Maleimide 2706-21.



F.W. = 123.11	104.06	225.15
50 mg	50.8 mg	91.41 mg
0.406 mmole	0.488 mmole	0.406 mmole

We couldn't prepare solution 50 mg N-Vinyl Maleimide in 1 mL D_2O — NG!

In a NMR tube was placed 50 mg N-Vinyl Maleimide & add solution of 51.6 mg $NaHSO_3$ in 1.0 mL D_2O. Vortex & heat at 50°C water bath for 10 min, almost all was dissolved, filter off through pipet filter to another NMR tube & submit for NMR.
Results see p. 25 Back side.

Rx at RT very slow.

Rx #2 1 g N-Vinyl Maleimide (0.00812M) 2706-21 + solution 1.02 g $NaHSO_3$ in 20 mL bi-H_2O (0.0098 M)
Shake at 55°C from 4 p.m. over weekend.

Rx had very small amount of solid; Rx was filtered off & water was removed with 2 × 20 mL CH_3CN (at 60°C under water aspirator).
Got 1.71 g. yellowish residue (2706-26-1) or 93.4% from theory - theory yield 1.829 g.
Prepare 30 mg/0.7 mL D_2O for NMR (see p. 26 Back side)

To Page No. 27

Witnessed & Understood by me, Deb Swan Date Invented by Date
Recorded by G. Stehman

Exhibit 4

From Page No. 26

Product 2706-26-1, has some impurities, need be purified.

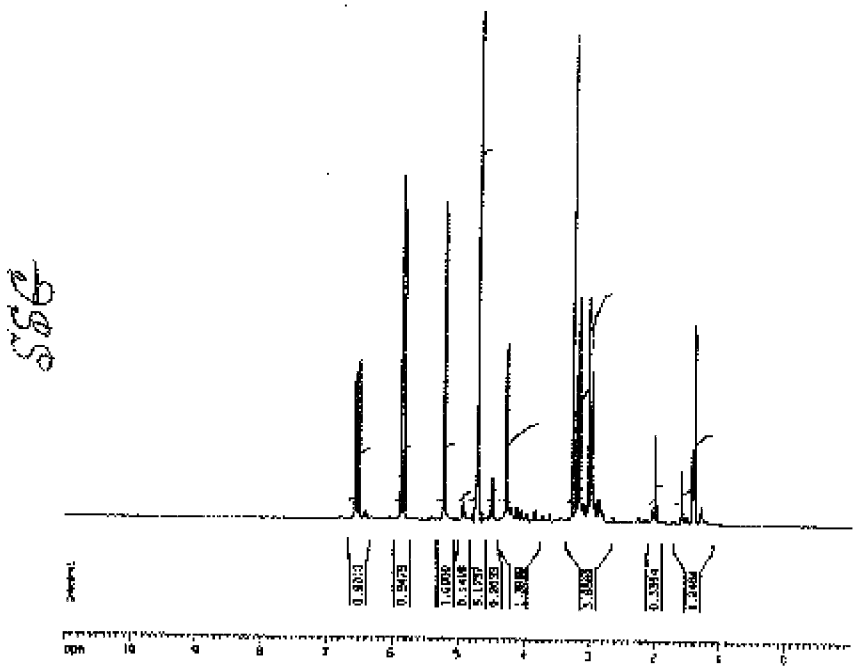
1.71 g 2706-26-1 was dissolved in 5.1 mL H_2O then was added 8 mL CH_3OH, heat at 60°C water bath. All was dissolved, cool solution in ice-water bath. Filter off solid, dry, at 60°C to gave 430 mg of offwhite crystals /2706-26-2/.

From filtrate we got 520 mg. offwhite crystals /2706-26-3/.

Prepare NMR samples.

2706-26-3 cleaner than 2706-26-1; 2706-26-2 impurity.

2706-26-3 was given to MJB for testing. DS



Witnessed & Understood by me, Date

Invented by Date

Recorded by

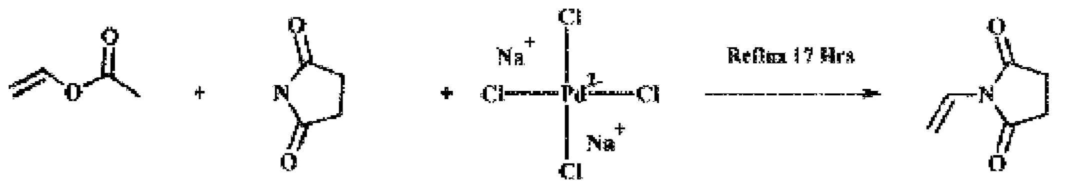
Exhibit 5

TITLE Vinyl-Succinimide

Project No. ITPM0100
Book No. 2706

From Page No. Ref. 2706-21

Vinyl-succinimide.SK2



26 30 mg

999.97 mg

86.089 g/mole	99.088 g/mole	294.210 g/mole	125.125 g/mole
3.55 g (~3.8 ml)	1.0 g	0.025 g	1.25 g (theory)
41.20 mmole	10.0 mmole	0.0085 mmole	10.0 mmole (theory)

In a 25 mL RB flask, with magnetic stir bar were placed all ingredient. Stir & heat to refluxing. Refluxing from 3.30 p.m.

7.10 a.m. - cool Rx. Filter off through pipet filter & wash with 2×5 mL CH_2Cl_2. Remove solvent on a Rotavap at 40°C under water aspirator with air bleeding in a flask. Got 1.3 g. yellow liquid. Add 4.5 mL Et_2O & stir in dry ice bath. Filter off solid, dry to gave 1.09 g. brownish solid / 2706-30/.

Prepare 30 mg/0.75 mL D_2O for NMR /see p. 29 back side/.

Product looks good by NMR.

TLC was developed in $CH_3OH/CHCl_3$ = 1/99 /see p. 29B/ & $CH_3OH/CHCl_3$ = 10/90.

We have one spot.

To Page No. 38

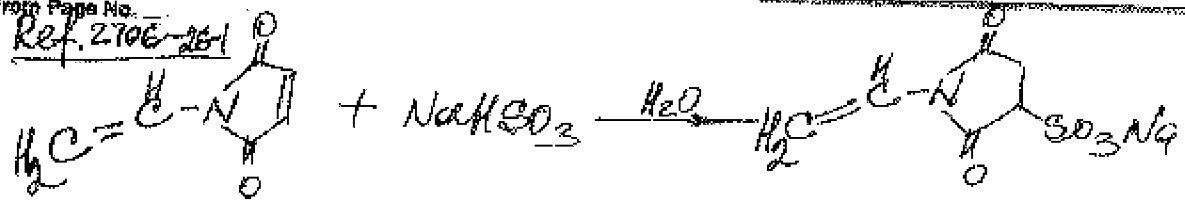
Witnessed & Understood by me,	Date	Invented by / Recorded by	Date
Dal Swo[illegible]		S. Stelman	/ /

Exhibit 6

TITLE Sulfo-N-Vinyl Succinimide Project No. TIPM0100
Book No. 2706 31

From Page No.

Ref. 2706-26!



125.11	104.06	225.15
1.0 g	1.02 g	1.828 g (theory)
0.00812 M	0.0098 M	0.00812 M (— u —)

To 1.0 g N-Vinyl Maleimide (#2706-21) was added solution 1.2 g $NaHSO_3$ in 20 mL bi-H_2O, was stirred 5 min then placed at 55°C oven on a Orbit Shaker & shaked from 2.15 p.m.

Prepare TLC, comparing Rx & starting material!

Water off Rx-solution was slightly cloudy. Remove water with 2 x 20 mL $CHCl_3$, dry on a Rotovap at 60°C to gave 1.67 g. Light yellow crystals /2706-31!

Prepare 30 mg/0.75mL D_2O for NMR (see p.30 back side).

Product is good.

500 mg was given to MJB for testing.

30 mg of 2706-31 was dissolved in 300uL bi-H_2O. Added 6.0 mL of Barium solution – no precipitation.

2.1 mL Methanol + 3 mL of Barium sol. → Nice precipitate.

③. 30 mg of 2706-31 was dissolved in 300uL bi-H_2O. Added 20 mL sat. K_2CO_3 – no precipitation.

To Page No.

Witnessed & Understood by me,
Dale Swan
Date

Invented by
Recorded by C. Stillman
Date

Exhibit 7

TITLE Sulfo-N-Vinyl Maleimide Succinimide Project No. TTPM0100

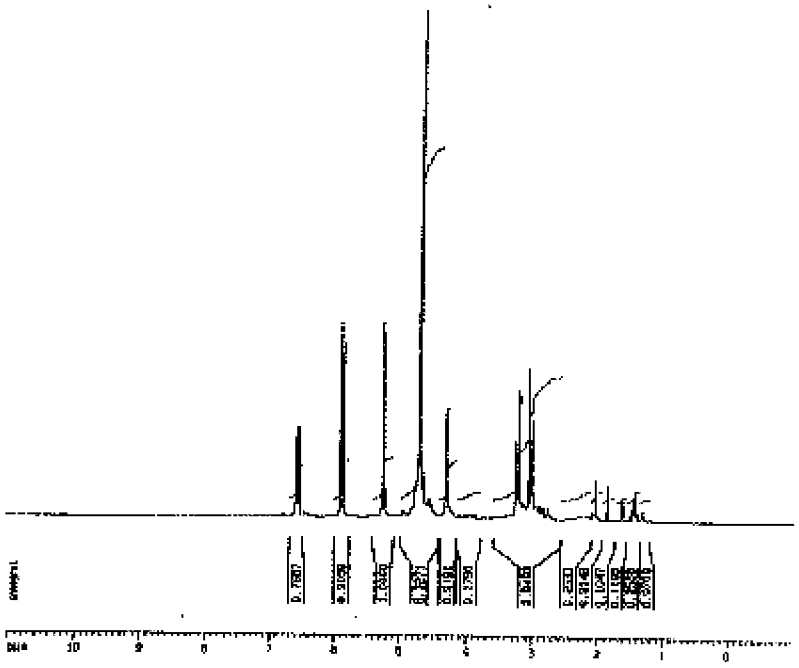
Book No. 2706 37

From Page No. Ref. 2706-31

To 1.75 g Vinyl-Maleimide (2706-21) was added 25 mL t-H$_2$O + 2.1 g NaHSO$_3$, vortex for 5 min, then shake ON at 55°C oven from 3.30 p.m.

Filter off foam insoluble. Remove water with 2×35 mL ethers, dry on a Rotovap at 60°C to gave 3.0 g. light yellow crystals (2706-37) (theory yield 3.2 g).

Product looks good - Was given to MB for testing.



To Page No.

Witnessed & Understood by me,

Date

Invented by

Recorded by D. Eckman

Date /

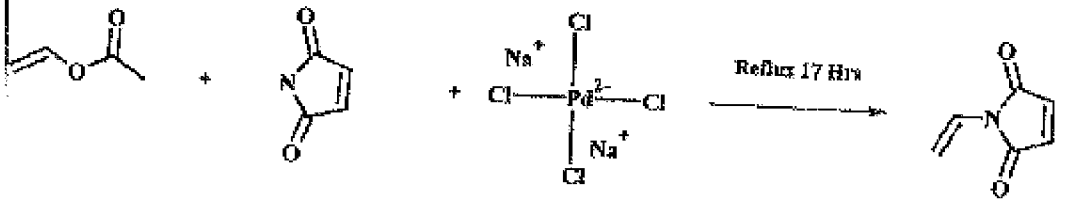
Exhibit 8

TITLE N-Vinyl Maleimide Project No. TPM0100
Book No. 2706 39

From Page No. Ref. 2706-21

SSG DS SSG

Vinyl-Maleimide.SK2



Acet. wt Maleimide 10.000g/5
Na2PdCl4 249.69g/m

86.089 g/mole	97.072 g/mole	294.210 g/mole	123.109 g/mole
35.5 g (~38 ml)	10 g	0.25 g	12.7 g (theory)
412.0 mmole	103.0 mmole	0.85 mmole	103.0 mmole (theory)

In a 100 ml RB flask with magnetic stir bar & reflux condenser were placed 10.000 g Maleimide (Lot # 90009987), 0.24969 g. Na_2PdCl_4 & 35.5 g. vinylacetate (Lot # 10224 DG). Stir & heat to refluxing. Refluxing started at 13.50 p.m. Boil. point of vinyl acetate = 72-73°C. T of oil bath = 85°C.

7.15 p.m. (~17.5 hours of refluxing) - remove oil bath, let cool, filter off from solid, remove excess of vinylacetate at 40°C with air bleeding in a flask. We got ~ 11.5 g. residue in the flask. Add 45 ml Et2O, stir in IPA-dry ice bath at T = -20°C for 30 min.

Filter off solid, dry at RT under water aspirator to gave 5.50 g. yellow crystals /2706-39/. Filtrate was stirred for 30 min more in IPA-dry ice bath at T = -20°C. Filter off, dry to gave 1.4 g. yellow crystals /39-1/. Ether was removed to gave 3.0 g. yellow /2706-39-2/

To Page No. 2-40

Witnessed & Understood by me.	Date	Invented by	Date	Back Side
Deb Swan		Recorded by D. Stehman		

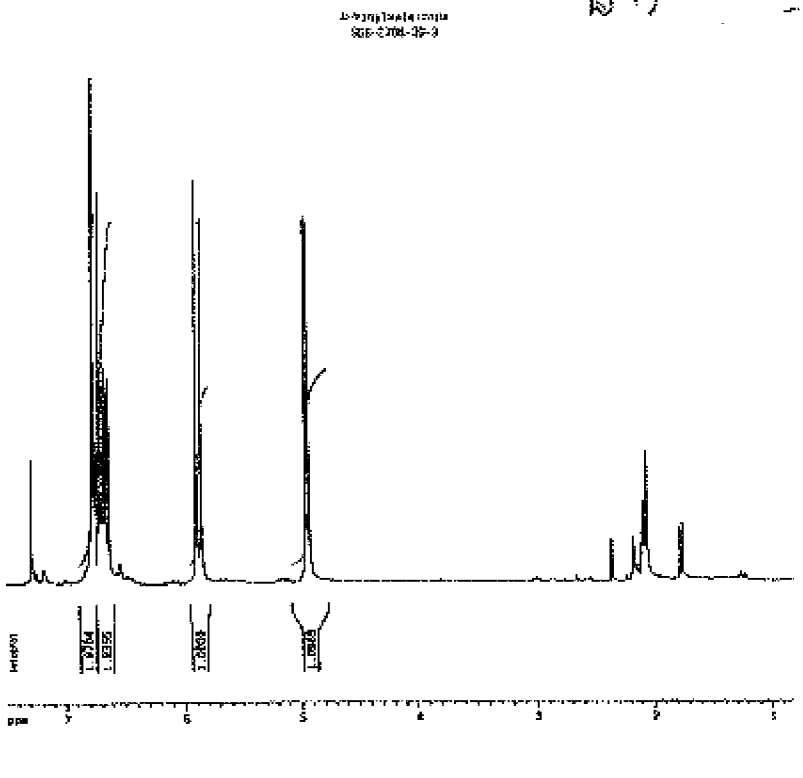
Exhibit 9

From p. 39.

solids (2706-39-2). Seems that product started to polymerize.

Redissolve solid (39-3) in 25 mL $CHCl_3$ by shaking on an Orbit Shaker for 20 min, filter off solids that didn't dissolve.

Remove $CHCl_3$ on a Rotovap at RT under water aspirator with air bleeding into a flask. Traces of solvent were removed by sweeping ON with air, to gave 1.41 g. yellow solid (2706-39-3).



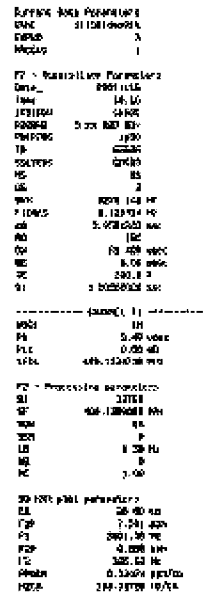
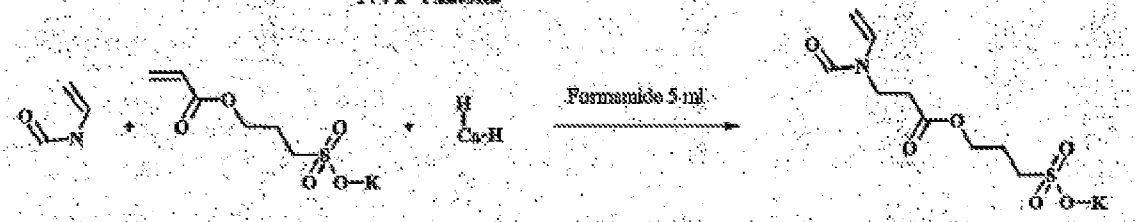


Exhibit 10

From Page No. see page 16-19

Purpose: to determine if X formamide would be a solvent for the reaction of N-Vinylformamide and the potassium salt of sulfopropyl acrylate.

NVF-rx2.sk2



1.014 g/ml N-vinylformamide (NVF)	Sulfopropylacrylate	Calcium hydride	
71.08 g/mole	232.30 g/mole	42.09 g/mole	303.38 g/mole
1.41 g (1.40 ml)	4.646 g	0.838 g	6.07 g (theory)
20.0 mmole	20.0 mmole	0.713 mmole	20.0 mmole (theory)

Procedure: The ingredients were stirred at an unknown temperature (25 to 90 C most likely). After 20 hours 0.1 ml was treated with 0.5 ml methanol and 0.5 ml chloroform. Removal of the volatiles gave 99 mg residue 2683-30-1 (mainly formamide any product?). The residue was washed with a second portion of methanol 0.5 ml and chloroform 0.5 ml. The clear liquid was again removed and evaporated to give 2683-30-2 (12.9 mg). The residue after two washings was dried to give 2683-30-3 (6.4 mg) Three samples were made for NMR comparisons- potassium sulfoacrylate 2683-30-4, formamide 2683-30-5, and N-vinyl formamide 2683-30-6. A final reaction sample 0.1 ml worked up with methanol and chloroform was labeled 2683-30-7. Sample 1,2 and 7 appeared to show a new four lined NMR peak at ~6.95 ppm. This new NMR peak may be evidence for the presence of the desired product..

JCB

To Page No.

Witnessed & Understood by me.	Date	Invented by	Date
		Recorded by	

Exhibit 11

SurModics Intellectual Property and Proprietary Product Idea Form (2)

Originator(s) **Date**

Ron Ofstead and Dale Swan

Title/Key Words

N-vinylamides as accelerators in matrix formation

Reference (Personal Notes/Notebook Number and Pages)

2683-16,20,26

Brief Description

Cells can be covered with a protective hydrogel coating. The polymerization of PEG-triacrylate around the cells is accelerated by the addition of N-vinylamides. In addition the presence of sulfonate containing monomers (ie AMPS) have been useful in improving biocompatibility. The idea was to synthesize reagents containing N-vinylamides and sulfonate functionality. The attachment of figures 1 to 4 show the reactions used to make N-vinyl amides.

Advantages and Features

The materials proposed can be made in one or two steps from available materials. Preliminary tests indicated firm gels resulted from the cyclic products synthesized.

Reduced to Practice (Date/Notebook Number and Pages)

2706-21, 26, 30, 31, 37, 39 from

Submitted by

Signature	Printed Name	Originator(s)	Date
Dale Swan	DALE SWAN		
R. Ofstead	R. Ofstead		

Read and Understood by

Signature	Printed Name	Witness	Date
Anthony Dallmier	Anthony Dallmier		
Jerome A. Behrens	Jerome A. BEHRENS		

PROPRIETARY
SurModics, Inc.

Exhibit 12

Based on the two previous batches made [#1 looked great; #2 [illegible] worked in [illegible] system]

~~[illegible]~~ CMJ [illegible] a series of experiments to test the synthesis of the [illegible]. [illegible] up [illegible] solutions @ different levels of sulfo-[illegible]-succinimide.

Lot # 2703-1K-(1,2,3,4,&5)

[illegible] ~ 50mg of each. Added ~ 8mg of each to 3% HA, 0.28% [illegible] solution, & let mix for 1 hour on 37°C shaker (Amber vials labeled 1-5, to represent [illegible] - see previous page for [illegible] set-up)

After mixing, [illegible] 75 µl to [illegible], [illegible] for 4 [illegible]:

1) Soft, no matrix, bleaching
2) Soft, matrix, no bleaching
3) good, firm matrix,
4) "
5) " "

[illegible] solutions sat O/N @ Room Temperature. All solutions, when [illegible], [illegible]

[illegible] mixed O/N @ 37°C Shaker – when [illegible], solutions looked similar; #3 may have been a bit softer, but hard to tell.

Witnessed & Understood by me, [illegible] | Date | Invented by [illegible] | Date